

Sequential estimation for covariate-adjusted response-adaptive designs

Running headline: Sequential estimation for CARA designs

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Abstract

In clinical trials, a covariate-adjusted response-adaptive (CARA) design allows a subject newly entering a trial a better chance of being allocated to a superior treatment regimen based on cumulative information from previous subjects, and adjusts the allocation according to individual covariate information. Since this design allocates subjects sequentially, it is natural to apply a sequential method for estimating the treatment effect in order to make the data analysis more efficient. In this paper, we study the sequential estimation of treatment effect for a general CARA design. A stopping criterion is proposed such that the estimates satisfy a prescribed precision when the sampling is stopped. The properties of estimates and stopping time are obtained under the proposed stopping rule. In addition, we show that the asymptotic properties of the allocation function, under the proposed stopping rule, are the same as those obtained in the non-sequential/fixed sample size counterpart. We then illustrate the performance of the proposed procedure with some simulation results using logistic models. The properties, such as the coverage probability of treatment effect, correct allocation proportion and average sample size, for diverse combinations of initial sample sizes and tuning parameters in the utility function are discussed.

Key words: Covariate-adjustment, logistic regression, response-adaptive design, sequential estimation, stopping time, targeted drug, utility function

1. Introduction

From an ethical viewpoint, it is desirable to minimize the number of subjects allocated to inferior treatments in the course of a clinical trial without jeopardizing the generation of useful and meaningful statistical inferences. The response adaptive (RA) design in clinical trials (Zelen and Wei 1995 and Hu and Rosenberger 2006) is dedicated to this purpose. The advantage of an RA design is that the information collected from subjects previously entering the trial can be used to adjust the allocation probability so that a newly entering subject can have a better chance of being allocated to a superior treatment. Because of the sequential characteristic in this process, sequential statistical methods should be

used in order to efficiently analyze these kinds of data sets. Since data collected in this manner are no longer independent, sequential methods that rely on assumption of independent observations are not valid. Moreover, due to innovation in genomic technologies and the nature of developing targeted drugs (Simon and Maitournam 2005), it is natural to incorporate the information available on individual covariates that have a strong influence on responses to a model, since they may be associated with the efficacy of treatments. Hence, the existence of an interaction between treatment and covariate becomes a reasonable presumption as far as, for example, a targeted drug is concerned.

A situation where there is an interaction between covariates and treatments is illustrated in Figure 1. In this figure, a logistic model is used to describe the relation between responses to treatments and covariates, where the covariates are generated from two normal distributions with a mean-shift denoting two sub-populations. Traditionally, we use an RA design by assuming there is no treatment-covariate interaction effect; that is, the slopes of treatments effects are assumed to be equal. However, when a treatment-covariate interaction exists, as in Figure 1, this assumption is not valid, and the lines A and B in this Figure will not be parallel. This implies that a method that uses RA design will make incorrect treatment allocation, when such a non-ignorable interaction exists. In this situation, it is reasonable to assume that a CARA design should perform better than an RA design in terms of correct allocation proportions. However, up until now, little work has been done on CARA designs. Since Figure 1 is for illustration purposes, it depicts an extreme example of two treatments with opposite slopes. However, as long as the slopes of the treatment effects are not equal, the two treatments make a lot of difference for subjects with covariates located far from the intersection of the lines of the treatment effects. Thus, as long as a targeted drug or other adaptive treatment strategy is being used, this situation should not be ignored. In addition to the ethical considerations, this is a further good reason for considering a CARA design. Further discussion about the properties of RA and CARA designs can be found in, Bandyopadhyay, Biswas, and Bhattacharya (2007), Bandyopadhyay and De (2009), Hu and Rosenberger (2006) and so on.

Although the sequential characteristics of RA and CARA designs are clear, and the sequential sampling method, which allows the sample size to be determined based on

the observed information, is known to be an adequate choice for making efficient and valid statistical inference, most discussions in the literature to date have been limited to the asymptotic properties of different designs. Even when the idea of a stopping rule has been adopted, there has still been very little discussion of estimation under those stopping criteria. Zhang and Hu (2009), and Bandyopadhyay and De (2009) are two typical examples. In these two studies, only large scale simulation studies were conducted to compare the properties of their designs and to provide information regarding suitable sample sizes for their designs. In another example, Moler, Plo, and Miguel (2006) treated the allocation ruled by an urn model as a Robbins-Monro scheme, but the property of the stopping rule was still ignored. In addition, Thall and Wathen (2005) compared the CARA design to the balanced randomization design, however, the same stopping rule based on the balanced randomized design was applied to both designs, which is inappropriate as indicated in their paper.

As mentioned above and also in Hu and Rosenberger (2006), the sequential method is a natural choice for a CARA design based clinical trial; however, it is rare to find literature regarding the application of stopping rules for the sequential estimation procedure based on CARA designs, and the effective sample size for a clinical trial with adaptive design. The difficulties are mostly due to the adaptive nature of CARA designs, which make the classical approach, based on the assumption of independent observation, less useful. Besides the adaptive design, the adjustment of the allocation probability based on subject's covariate information makes the procedure even more complicated. Hence, the asymptotic properties of estimates under randomly stopped CARA experiments, derived in our paper, are not trivial and cannot follow from their non-random sample size counterpart.

In this paper, a sequential procedure is proposed for estimating treatment effect under a general CARA design. Our goal is to estimate the treatment effects, with the minimum sample size, such that the estimates satisfy a prescribed precision, and subjects can be allocated to the superior treatment without interfering with the the quality and efficiency of estimation of treatment effects. The asymptotic properties of sequential estimates are obtained under this general CARA design. In addition, we also show that the allocation

rule, under the proposed stopping criterion, maintains the same asymptotic properties as those obtained in its non-sequential counterpart. In our numerical study, for illustration purposes, we adopt the method of Bandyopadhyay et al. (2007) and use a utility function to balance the ethical consideration and the efficiency of the estimate for treatment allocation. We, then, modify the utility function to vary the tuning parameters sequentially depending on the precision of the estimate at every allocation stage such that subjects are allocated to a “more adequate” treatment.

The rest of this paper is organized as follows: A sequential estimation procedure for treatment effect is proposed in Section 2. Simulation results are applied to logistic models using a modified allocation rule (Bandyopadhyay, Biswas, and Bhattacharya 2007) in Section 3. We, then, conclude with discussion in Section 4. Proofs of theorems are given in the Appendix.

2. Sequential Estimation of Treatment Effect

Let $N_{m,k}$ be the number of subjects assigned to treatment k during the first m assignments and $\mathbf{N}_m = (N_{m,1}, \dots, N_{m,K})$. Suppose that $\{Y_{m,k}, m = 1, 2, \dots, k = 1, \dots, K\}$ denotes responses of the m -th subject to the k -th treatment and $\mathbf{Y}_m = (Y_{m,1}, \dots, Y_{m,K})$. Let $\boldsymbol{\xi}_m$ be the covariates of the m -th subject. Suppose that $\mathbf{X}_1, \mathbf{X}_2, \dots$ is the sequence of random treatment assignments, and $\mathbf{X}_m = (X_{m,1}, \dots, X_{m,K})$, $X_{m,k} \in \{0, 1\}$, denotes assignment of treatment k to the m -th subject. Then $X_{m,k} = 1$ for some k and $\sum_{k=1}^K X_{m,k} = 1$. That is, each subject is allocated to one treatment only. Hence, it follows that the response of subject m to the treatment k , $Y_{m,k}$, is observed only if $X_{m,k} = 1$. (Note that this implies that $\mathbf{N}_m = \sum_{i=1}^m X_{i \cdot}$)

Define $\mathcal{X}_m = \sigma(\mathbf{X}_1, \dots, \mathbf{X}_m)$, $\mathcal{Y}_m = \sigma(\mathbf{Y}_1, \dots, \mathbf{Y}_m)$, and $\mathcal{Z}_m = \sigma(\boldsymbol{\xi}_1, \dots, \boldsymbol{\xi}_m)$, $\boldsymbol{\xi}_i \in \mathbb{R}^p$, be the corresponding σ -fields. Let $\mathcal{F}_m = \sigma(\mathcal{X}_m, \mathcal{Y}_m, \mathcal{Z}_m)$, then a general CARA design is defined as

$$\psi_m = E[\mathbf{X}_m | \mathcal{F}_{m-1}, \boldsymbol{\xi}_m] = E[\mathbf{X}_m | \mathcal{X}_{m-1}, \mathcal{Y}_{m-1}, \mathcal{Z}_m.]$$

Suppose that for each $m \geq 1$, the responses and covariate vector satisfy

$$E[Y_{m,k}|\boldsymbol{\xi}] = \mu_k(\theta_k, \boldsymbol{\xi}), \quad (1)$$

where $\mu_k(\cdot, \cdot)$ are known functions, V_k denotes the covariance matrix based on Equation (1) and $\theta_k \in R^p$ for $k = 1, \dots, K$. The asymptotic properties of the estimate of $\boldsymbol{\theta} = (\theta_1, \dots, \theta_K)$ and allocation function under such a general CARA design has been discussed in Zhang et al. (2007). The estimation of θ is the primary goal in a clinical trial. Thus, it will be beneficial if treatment effects can be estimated with a certain accuracy using a minimum required sample size whilst simultaneously still retaining the good allocation properties. Since, in a CARA design, the design at the current stage depends on the past history, sequential analysis is the statistical tool of choice. Here a sequential estimation procedure is proposed for constructing a confidence set for θ with a prescribed accuracy, and we show that the asymptotic properties of allocation function remain the same as their non-sequential counterparts under such a sequential sampling strategy.

Suppose no prior information about the effects of treatments is available. In order to estimate the treatment effects, at the beginning, we need to assign $m_0(> 0)$ subjects to each treatment using restricted randomization. Hence, when we allocate the m -th subject ($m > Km_0$), there are already $m - 1$ observations, $\{(\mathbf{X}_1, \mathbf{Y}_1, \boldsymbol{\xi}_1), \dots, (\mathbf{X}_{m-1}, \mathbf{Y}_{m-1}, \boldsymbol{\xi}_{m-1})\}$, collected. Thus, we assign the m -th subject to the treatment k with probability

$$\psi_k = P(X_{m,k} = 1 | \mathcal{F}_{m-1}, \boldsymbol{\xi}_m) = \pi_k(\hat{\theta}_{m-1}, \boldsymbol{\xi}_m),$$

where $\hat{\theta}_{m-1}$ is the maximum quasi-likelihood estimate of θ based on the previous $m - 1$ observations and $\pi_k(\cdot, \cdot)$ is the true allocation probability for treatment k and the given covariate. Assume further that $\mu_k(\theta_k, \boldsymbol{\xi}_m) = \mu_k(\boldsymbol{\xi}_m' \theta_k)$ for each $m \geq 1$. Hence, it follows from Equation (1) and V , that the method of generalized linear models (quasi-likelihood) can be applied (McCullagh and Nelder 1989). Assume that $\theta_k \in \Theta_k \subseteq R^p$ is bounded for $k = 1, \dots, K$, and let the parameter space $\Theta = \prod_{k=1}^K \Theta_k$.

Under the above assumptions (see also Condition A of Zhang et al. (2007), Theorem

2.1), it is proved that as $\min(N_{m,k}, k = 1, \dots, K)$ goes to infinity,

$$\sqrt{n}(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}) \rightarrow_{\mathcal{L}} N(0, \mathbf{V}),$$

where $\mathbf{V} = \text{diag}\{V_1, \dots, V_K\}$. Based on the asymptotic normality of $\hat{\boldsymbol{\theta}}$, the sequential method is employed for estimating the confidence set of $\boldsymbol{\theta} = (\theta_1, \dots, \theta_K)$. Define

$$R = \{\boldsymbol{\theta} \in \Theta : n(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta})' \mathbf{V}^{-1} (\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}) \leq C_\alpha^2\},$$

where C_α^2 is the constant such that $P(\chi^2(p \cdot K) \geq C_\alpha^2) \leq \alpha$. The asymptotic normality of $\hat{\boldsymbol{\theta}}$ implies that $P(\boldsymbol{\theta} \in R) \approx 1 - \alpha$ as the sample size becomes large.

Although large sample results guarantee the performance of estimates and some asymptotic properties of CARA designs, we want to know just how large a sample size is needed to guarantee a satisfactory performance in a practical sense. Moreover, no matter how high the coverage probability is, the confidence set becomes less useful if the size of the confidence set becomes too large. Now, suppose we further require that the maximum axis of R is no larger than 2δ for some $\delta > 0$, then the minimum sample size to achieve this goal is

$$n\Lambda_{\min}(\mathbf{V}^{-1}) \geq \frac{C_\alpha^2}{\delta^2}.$$

Equivalently, the above inequality can be re-written as

$$n \geq \frac{C_\alpha^2 \Lambda_{\max}(\mathbf{V})}{\delta^2}, \tag{2}$$

where notations $\Lambda_{\max}(A)$ and $\Lambda_{\min}(A)$ denote the maximum and minimum eigenvalues of matrix A , respectively. Let R_δ denote the corresponding confidence ellipsoid for given δ . So, once $\delta > 0$ is specified, the maximum axis of confidence ellipsoid R_δ is no greater than 2δ . The constant δ here is used as a measure of precision of the confidence ellipsoid R_δ . Please refer to Siegmund (1985), Albert (1966) and Ghosh and Sen (1991) for other measures of confidence sets.

If \mathbf{V} is known, then the optimal sample size required to construct a confidence ellipsoid

R_δ with the required maximum axis no greater than 2δ is

$$n_{opt} = \text{first } n \text{ such that } n \geq \frac{C_\alpha^2 \Lambda_{\max}(\mathbf{V})}{\delta^2}.$$

Since the variance matrix \mathbf{V} is usually unknown, the above optimal sample size is not available. Replacing the unknown \mathbf{V} in Equation (2) with its consistent estimate $\hat{\boldsymbol{\theta}}$ (to be defined later), a stopping rule to construct such a fixed size confidence ellipsoid is suggested:

$$\begin{aligned} \tau_\delta &= \text{first } n \text{ such that } n \geq \frac{C_\alpha^2 \Lambda_{\max}(\hat{\mathbf{V}})}{\delta^2} \\ &= \inf\{n \geq n_0 : n \geq \frac{C_\alpha^2 \Lambda_{\max}(\hat{\mathbf{V}})}{\delta^2}\}, \end{aligned} \quad (3)$$

where $n_0 \geq Km_0$ is the minimum initial sample size and m_0 is the initial sample size for each treatment. Similarly, we then define

$$\hat{R}_\delta = \{\boldsymbol{\theta} \in \Theta : n(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta})' \hat{\mathbf{V}}^{-1} (\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}) \leq C_\alpha^2\}.$$

It follows from the strong consistency of $\hat{\boldsymbol{\theta}}$, if $\hat{\mathbf{V}}$ is also a strongly consistent estimate of \mathbf{V} , then $\lim_{n \rightarrow \infty} P(\boldsymbol{\theta} \in \hat{R}_\delta) = 1 - \alpha$. That is, \hat{R}_δ is a confidence ellipsoid of $\boldsymbol{\theta}$ with coverage probability $1 - \alpha$, asymptotically.

It follows from the definition of τ_δ that, when the sequential sampling stops, the confidence ellipsoid will have its maximum axis no greater than 2δ . However, it is also known that there is no guarantee that $\hat{\boldsymbol{\theta}}$ will have the same asymptotic distribution if we replace the fixed sample size with a random sample size τ_δ . Although the sequential estimation procedure provides a way to control the size of the confidence set by utilizing a stopping rule, it is interesting to know whether the asymptotic properties in Zhang et al. (2007) are still adhered to under such a randomly stopped criterion.

Suppose that allocation function $\boldsymbol{\pi}(\cdot, \cdot) = (\pi_1(\cdot, \cdot), \dots, \pi_K(\cdot, \cdot))$ and satisfies the following conditions:

$$(C1) \sum_{k=1}^K \pi_k = 1 \text{ and } 0 < \nu_k = E_{\boldsymbol{\xi}}[\pi_k(\boldsymbol{\theta}, \boldsymbol{\xi})] < 1, k = 1, \dots, K.$$

(C2) For fixed $\boldsymbol{\xi}$, $\pi_k(\boldsymbol{\theta}, \boldsymbol{\xi}) > 0$ is a continuous function of $\boldsymbol{\theta}$ and is differentiable with respect to $\boldsymbol{\theta}$ such that $\nu_k(\tilde{\boldsymbol{\theta}}) = \nu_k(\boldsymbol{\theta}) + (\tilde{\boldsymbol{\theta}} - \boldsymbol{\theta})(\partial \nu_k / \partial \tilde{\boldsymbol{\theta}})' + o(\|\tilde{\boldsymbol{\theta}} - \boldsymbol{\theta}\|^{1+\zeta})$ for some $\zeta > 0$.

The condition $\pi_k > 0$ for each $k = 1, \dots, K$ on the allocation function guarantees that subjects will be allocated to individual treatments, eventually. Thus, this condition also affirms that with probability one the design matrix is non-singular, and the $\Lambda_{\min}(\mathbf{V}^{-1}) > 0$, asymptotically. Under these conditions, in Theorem 1, we show that the sequential procedure with the stopping rule defined in (3) can guarantee that the size of the maximum axis of confidence ellipsoid is no greater than the pre-specified length, while maintaining the required coverage probability. In addition to classical asymptotic properties of sequential confidence set estimation, the asymptotic properties of the allocation function under sequential sampling that is based on the CARA design are also proved in Theorem 1.

Theorem 1 *Under some regularity conditions on the link function μ_k and Conditions (C1) and (C2) for the allocation function ν_k , for each k , if $\sup_m \|\boldsymbol{\xi}_m\| < \infty$, then the proposed sequential estimation with the stopping rule defined in (3) has the following properties:*

(i) $P(\tau_\delta < \infty) = 1$ and $\lim_{\delta \rightarrow 0} \tau_\delta / n_{opt} = 1$ almost surely.

When the sampling stops, the estimate of $\boldsymbol{\theta}$ satisfies that

(ii) $\hat{\boldsymbol{\theta}}_{\tau_\delta} \rightarrow \boldsymbol{\theta}$ almost surely as $\delta \rightarrow 0$, $\sqrt{\tau_\delta}(\hat{\boldsymbol{\theta}}_{\tau_\delta} - \boldsymbol{\theta}) \rightarrow_{\mathcal{L}} N(0, V)$, and $\lim_{\delta \rightarrow 0} P(\boldsymbol{\theta} \in R_\delta) = 1 - \alpha$.

Then, in addition, the average of the stopping rule satisfies that

(iii) $\lim_{\delta \rightarrow 0} E \left[\frac{\tau_\delta}{n_{opt}} \right] = 1$.

Moreover, for a given allocation function, it is shown that

(iv) $\lim_{\delta \rightarrow 0} \frac{\mathbf{N}_{\tau_\delta}}{\tau_\delta} = \boldsymbol{\nu}$ almost surely,

(v) $\frac{N_{\tau_\delta, k | \boldsymbol{\xi}}}{N_{\tau_\delta | \boldsymbol{\xi}}} \rightarrow \pi_k(\boldsymbol{\theta}, \boldsymbol{\xi})$ a.s. as $\delta \rightarrow 0$, $k = 1, \dots, K$, and

$$(vi) \sqrt{\tau_\delta}(\mathbf{N}_{\tau_\delta}/\tau_\delta - \boldsymbol{\nu}) \rightarrow_{\mathcal{L}} N(\mathbf{0}, \boldsymbol{\Sigma}),$$

where $N_{\tau_\delta, k|\boldsymbol{\xi}}$ is the number of subjects assigned to treatment k with covariate $\boldsymbol{\xi}$ up to τ_δ th subject and $N_{\tau_\delta|\boldsymbol{\xi}}$ is the total number of subjects with covariate $\boldsymbol{\xi}$ up to τ_δ th subject. Here $\boldsymbol{\nu} = (\nu_1, \dots, \nu_K)'$ and π_k , $k = 1, \dots, K$, depend on the allocation function, and $\boldsymbol{\Sigma} = \boldsymbol{\Sigma}_1 + 2\boldsymbol{\Sigma}_2$ where $\boldsymbol{\Sigma}_1 = \text{diag}\{\boldsymbol{\nu}\} - \boldsymbol{\nu}'\boldsymbol{\nu}$ and $\boldsymbol{\Sigma}_2 = \sum_{k=1}^K (\frac{\partial \boldsymbol{\nu}}{\partial \theta_k}) V_k (\frac{\partial \boldsymbol{\nu}}{\partial \theta_k})'$.

Theorem 1 (i) states that the sequential sampling will stop eventually, and (ii) and (iii) are named asymptotic consistency and efficiency of a sequential confidence estimation procedure by Chow and Robbins (1965). Theorem 1 (iii) means that the average ratio of the sequential sample size to optimal sample size converges to 1. This means the proposed sequential sampling is efficient in terms of sample size used for constructing a fixed size confidence ellipsoid of the parameters of interest.

Theorem 1 (iv) to (vi) provides the asymptotic properties of the allocation rule under the sequential estimation procedure. In particular, Theorem 1 (iv) states that eventually the allocation proportion converges to the allocation expectation $\boldsymbol{\nu}$, and Theorem 1 (v) states that for the given covariate $\boldsymbol{\xi}$, the proportion of allocation converges to the “true” (unknown) allocation probability with probability one as δ goes to zero. That is, if the conditions in Theorem 1 are satisfied, then under the proposed sequential sampling method, the allocation rule maintains the same asymptotic properties as those in its non-sequential sampling counterpart. In our simulation study, we have demonstrated our procedure using the allocation rule proposed in Bandyopadhyay et al. (2007). Please refer to Zhang et al. (2007) for different allocation functions/designs under this general framework.

Remark 1 *Note that the proof of the properties of the sequential procedure is not trivial, and cannot follow directly from the results of the estimates based on the non-random sample size case due to the application of the stopping rule. This can be seen from a simple example in Chow and Teicher (1988) (Chapter 4, Example 1, page 90). Since our proof of Theorem 1 is based on the last time approach of Chang (1999), some conditions on the parameter space Θ can be relaxed. Details are given in the Appendix.*

2.1 Subset of parameters

Sometimes, we are only interested in contrasts of parameters. For example, instead of estimating individual treatment effects, we may want to estimate differences between treatment effects in a clinical trial with multiple treatments. For this purpose, let H be a $p \times h$ matrix that specifies the contrasts with $0 < \text{Rank}(H) = h \leq p$. Let $\boldsymbol{\gamma} = H'\boldsymbol{\theta}$, then the asymptotic properties of $\hat{\boldsymbol{\theta}}$ imply that as $n \rightarrow \infty$

$$\sqrt{n}(\hat{\boldsymbol{\gamma}}_n - \boldsymbol{\gamma}) \rightarrow_{\mathcal{L}} N(0, \mathbf{V}_{\boldsymbol{\gamma}}),$$

where $V_{\boldsymbol{\gamma}} = H'\mathbf{V}H$. Let $\hat{\mathbf{V}}_{\boldsymbol{\gamma}} = H'\hat{\mathbf{V}}H$. Then $\hat{\mathbf{V}}_{\boldsymbol{\gamma}}$ is a strongly consistent estimate of $\mathbf{V}_{\boldsymbol{\gamma}}$. Therefore, it follows that $n(\hat{\boldsymbol{\gamma}} - \boldsymbol{\gamma})'\hat{\mathbf{V}}_{\boldsymbol{\gamma}}^{-1}(\hat{\boldsymbol{\gamma}} - \boldsymbol{\gamma})$ is asymptotically distributed with $\chi^2(h)$. Let

$$R_{\delta_{\boldsymbol{\gamma}}} = \{\boldsymbol{\gamma} \in R^h : n(\hat{\boldsymbol{\gamma}} - \boldsymbol{\gamma})'\mathbf{V}_{\boldsymbol{\gamma}}^{-1}(\hat{\boldsymbol{\gamma}} - \boldsymbol{\gamma}) \leq C_{\alpha, \boldsymbol{\gamma}}^2\} \quad (4)$$

Similarly, we can also construct a confidence ellipsoid of $\boldsymbol{\gamma}$ with the length of its maximum axis no greater than $2\delta_{\boldsymbol{\gamma}}$. Then the optimal sample size and its corresponding stopping time are

$$n_{\boldsymbol{\gamma}, \text{opt}} = \text{first } n \text{ such that } n \geq \frac{C_{\alpha, \boldsymbol{\gamma}}^2 \Lambda_{\max}(\mathbf{V}_{\boldsymbol{\gamma}})}{\delta_{\boldsymbol{\gamma}}^2} \quad (5)$$

and

$$\tau_{\delta_{\boldsymbol{\gamma}}} = \inf\{n \geq n_0 : n \geq \frac{C_{\alpha, \boldsymbol{\gamma}}^2 \Lambda_{\max}(\hat{\mathbf{V}}_{\boldsymbol{\gamma}})}{\delta_{\boldsymbol{\gamma}}^2}\}. \quad (6)$$

By simple matrix algebra, we have a parallel theorem to Theorem 1 for contrasts of parameters.

Theorem 2 *Let H be a $p \times h$ matrix with $\text{Rank}(H) = h \leq p$, and $\boldsymbol{\gamma} = H'\boldsymbol{\theta}$. Then under conditions similar to Theorem 1, $\hat{\boldsymbol{\gamma}}$ is a strongly consistent estimate of $\boldsymbol{\gamma}$ and asymptotically normally distributed with covariance matrix $\mathbf{V}_{\boldsymbol{\gamma}} = H'\mathbf{V}H$. Moreover, the sequential procedure with the stopping rule defined in (6) has the following asymptotical*

properties:

(i) $P(\tau_{\delta_\gamma} < \infty) = 1$ and $\lim_{\delta_\gamma \rightarrow 0} \tau_{\delta_\gamma} / n_{\gamma, opt} = 1$ almost surely.

(ii) $\hat{\gamma}_{\tau_{\delta_\gamma}} \rightarrow \gamma$ almost surely as $\delta_\gamma \rightarrow 0$, $\sqrt{\tau_{\delta_\gamma}}(\hat{\gamma}_{\tau_{\delta_\gamma}} - \gamma) \rightarrow_{\mathcal{L}} N(0, \mathbf{V}_\gamma)$, and $\lim_{\delta_\gamma \rightarrow 0} P(\gamma \in R_{\delta_\gamma}) = 1 - \alpha$.

(iii) $\lim_{\delta_\gamma \rightarrow 0} E \left[\frac{\tau_{\delta_\gamma}}{n_{\gamma, opt}} \right] = 1$,

where R_{δ_γ} and $n_{\gamma, opt}$ are defined in (4) and (5), respectively.

The main difference between the new stopping rule defined in Equation(6) and the previous one is the variance of $\hat{\gamma}$, and this difference in τ_{δ_γ} does not affect the allocation rule. Therefore, the asymptotic properties of the allocation rule in Theorem 2 follow from the same arguments as in the proof of Theorem 1. In fact, the asymptotic properties of the allocation rule remain the same under this stopping rule, and are not re-stated here. That is, this sequential estimation procedure allows us to compare treatment effects using a contrast estimation method under a CARA design without disturbing the asymptotic properties of the allocation function, which is a useful feature in practice.

Remark 2 *Note that the asymptotic properties of the allocation function in Theorem 2 will remain the same as those in Theorem 1 when δ_γ becomes small. However, intuitively, the sequential sample sizes should converge at different rates, depending on the contrasts. This property is usually reflected in the second order term of the stopping time and is not shown in Theorem 2.*

3. Numerical Study

The purpose of the numerical study is to look at the performance of the estimate of the treatment effect and the allocation of subjects. In order to apply the sequential confidence estimation procedure proposed in Section 2 for K treatments, and treatment allocation procedures in Section 3.1, for illustration purposes, we consider a binary response case in this study using the logistic model.

3.1 Treatment Allocation Rule

In order to skew the treatment allocation proportion so that the better treatment is allocated more often, Bandyopadhyay et al. (2007) suggests using an utility function below. For K treatments, their utility function is defined as

$$U(p) = \log |\hat{I}_{n+1}| - \eta \left\{ \sum_{k=1}^K p_k \log \left(\frac{p_k}{\pi_k(\hat{\boldsymbol{\theta}}, \boldsymbol{\xi})} \right) \right\}, \quad (7)$$

where $\pi_k(\hat{\boldsymbol{\theta}}, \boldsymbol{\xi})$ is the estimate of $\pi_k(\boldsymbol{\theta}, \boldsymbol{\xi})$ denoting the estimate of the allocation probability for treatment k up to current stage n . For a given $\boldsymbol{\xi}$ and the current estimate of $\boldsymbol{\theta}$, the optimal allocation rule is to find the vector of probabilities $\mathbf{p} = (p_1, \dots, p_K)$ that maximize the utility function above. That is, the design at the $(n+1)$ th stage is to allocate the $(n+1)$ th subject to the treatment that maximizes the utility function.

In the utility function, the first term is in $\log n$ scale, which is a log determinant of the information matrix. If $\eta = 0$, then the new subject is selected to maximize the Fisher information matrix, which is referred to as the piecewise D-optimal design as mentioned in Bandyopadhyay et al. (2007). On the other hand, if η goes to ∞ , then the optimal value of p is to maximize the relative entropy function, the second term of (7), which was also raised in Bandyopadhyay and Biswas (2001). Hence, the parameter η can be used to adjust the ethical and efficiency balance. Here we use a utility function to balance the needs for estimation precision of treatment effects and the ethical consideration. It leads to the (locally) D-optimal design.

At the beginning of a study, when estimates of treatment effects are not reliable, we can improve the precision of the estimation of treatment effects when allocating patients via a utility function. Since the estimate of treatment effects becomes stable as the sample size becomes large, it is reasonable to move the weight gradually toward the ethical part at the later stage of the study. If there is sufficient information on treatment effects, we tend to allocate more patients to the better treatment. That is, unlike the two-stage design in Bandyopadhyay et al. (2007), we now have more flexibility to alter the parameters of the utility function as sampling goes on such that the needs for estimating treatment effects and the ethical consideration can be fulfilled and balanced.

The second term in the utility function involves $\pi_k(\hat{\boldsymbol{\theta}}, \boldsymbol{\xi})$. Modifying the utility function by Bandyopadhyay et al. (2007), $\pi_k(\hat{\boldsymbol{\theta}}, \boldsymbol{\xi})$ can be defined as follows with $K = 2$ for illustration purposes.

$$\pi_1(\hat{\boldsymbol{\theta}}, \boldsymbol{\xi}) = J\left(\frac{\boldsymbol{\xi}'\hat{\boldsymbol{\theta}}_1 - \boldsymbol{\xi}'\hat{\boldsymbol{\theta}}_2}{T_n}\right) \quad \text{and} \quad \pi_2(\hat{\boldsymbol{\theta}}, \boldsymbol{\xi}) = 1 - \pi_1(\hat{\boldsymbol{\theta}}, \boldsymbol{\xi}),$$

where $J(t)$ can be any symmetric function. $\pi_k(\hat{\boldsymbol{\theta}}, \boldsymbol{\xi})$ can vary sequentially through T_n at each allocation. Both T_n and η can serve as tuning parameters between efficiency and ethics and be random depending on the estimate precision, which can be a function of standard deviation of the treatment effect estimate based on cumulative observations up to n th subject. Please note that T_n and η are also tuned by a new covariate ξ of the $(n + 1)$ th subject. Through numerical studies, Bandyopadhyay et al. (2007) provides tables with estimates of allocation proportions for several η s and given T_n for two stage CARA designs. In Section 3.2, we present numerical results with some suggestions for tuning both parameters of T_n and η , and the proposed sequential procedure is also evaluated with its correct allocation probability.

3.2 Application to Logistic Models

Suppose $Y_k = 1(0)$ denotes a response variable with success (failure) from a subject assigned to treatment k for $k = 1, \dots, K$. Let $\mu_k(\theta_k, \boldsymbol{\xi}) = E[Y_k = 1 | \boldsymbol{\xi}]$, and $\theta_k = (\alpha_k, \theta_k^*)$. Assume that

$$\text{logit}(\mu_k(\theta_k, \boldsymbol{\xi})) = \alpha_k + \theta_k^* \boldsymbol{\xi}, k = 1, \dots, K. \quad (8)$$

Since the covariate vector can be redefined as $(1, \boldsymbol{\xi})'$, without loss of generality, we assume that $\alpha_k = 0$, $k = 1, \dots, K$. Suppose there are m_0 initial samples for each treatment and assume that we are at the m th stage with $m > Km_0$. Then the MLE $\hat{\theta}_{m,k}$ of θ_k , for

$k = 1, \dots, K$, is the one that maximizes

$$L_k = \prod_{i=1}^m \mu_{i,k}^{X_{i,k}} (1 - \mu_{i,k})^{X_{i,k}(1-Y_{i,k})}, \quad (9)$$

where $\mu_{i,k} = \mu_k(\theta_k, \boldsymbol{\xi}_i)$. It follows that the conditional Fisher information matrix, for given $\boldsymbol{\xi}$, is

$$I_k(\theta_k | \boldsymbol{\xi}) = \mu_k(\theta_k, \boldsymbol{\xi})(1 - \mu_k(\theta_k, \boldsymbol{\xi}))\boldsymbol{\xi}\boldsymbol{\xi}'.$$

Let $\hat{I}_{n,k} = n^{-1} \sum_{i=1}^n X_{i,k} I_k(\hat{\theta}_{n,k} | \boldsymbol{\xi}_i)$ be the estimate of I_k for all k . Then for a K treatments problem, for example, the new design is chosen such that the Fisher information matrix \hat{I}_{n+1} is maximized, if we assume $\eta = 0$, where $\hat{I}_{n+1} = \hat{I}_n + \hat{I}^{n+1}$,

$$\begin{aligned} \hat{I}_n &= \begin{pmatrix} \frac{1}{n} \sum_{i=1}^n X_{i,1} \hat{\lambda}_{i,1} \boldsymbol{\xi}_i \boldsymbol{\xi}_i' & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & \frac{1}{n} \sum_{i=1}^n X_{i,K} \hat{\lambda}_{i,K} \boldsymbol{\xi}_i \boldsymbol{\xi}_i' \end{pmatrix}, \\ \hat{I}^{n+1} &\equiv \begin{pmatrix} p_1 \hat{\lambda}_{j,1} \boldsymbol{\xi}_j \boldsymbol{\xi}_j' & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & p_K \hat{\lambda}_{j,K} \boldsymbol{\xi}_j \boldsymbol{\xi}_j' \end{pmatrix}, \end{aligned} \quad (10)$$

and $\hat{\lambda}_{i,k} = \hat{\mu}_{i,k}(1 - \hat{\mu}_{i,k})$ for $i = 1, \dots, n$, $j = n+1$, and $k = 1, \dots, K$.

3.2.1 Parameter Setup and Simulation Results

Suppose that $K = 2$; that is, we assume logistic models with binary responses, two treatments and one continuous covariate ξ . In the logistic models, we assume equal intercepts for both treatments $(\alpha_1, \alpha_2) = (0.1, 0.1)$ and regression coefficients $(\theta_1^*, \theta_2^*) = (-1, 1)$. The covariate is generated from a mixed normal distribution with means 2 & -2 and equal variance 1 with respective probability 0.5. Since the treatment effect is defined as a function of differences of intercepts and regression coefficients between the two treatments, we apply the stopping rule for the contrasts of parameters, $\boldsymbol{\gamma} = H' \boldsymbol{\theta}$, given in Section 2.1. Thus, the transpose of the contrast H is defined as a matrix with its first row $(1, -1, 0, 0)$ and its second row $(0, 0, 1, -1)$, and the vector of parameters $\boldsymbol{\theta}$

is $(\alpha_1, \alpha_2, \theta_1^*, \theta_2^*)'$.

Precision δ is assumed 0.3 and initial sample size for each treatment, m_0 , is assumed as 5, 10, and 15. Several combinations of tuning parameters T_0 and η are assumed: 0.5, 1 and 2 for T_0 and 0, 0.1 and 1 for η . Both fixed and varying tuning parameters, T_0 and η , are considered; that is, T_0 and η are fixed until the study stops, or vary whenever a new observation is added in a way that T_0 is proportional and η is inversely proportional to the standard deviation of the treatment effect for a given covariate of a new observation. Findings from simulation studies are as follows:

As η gets larger, stopping time gets larger but its increase is reduced as initial sample size gets larger. Varying η does not give results that are significantly different from fixed η unless T_0 varies as well. Stopping time is very unstable when initial sample size m_0 is small, such as 5, due to unstable regression coefficient estimates at the beginning stage if T_0 is 0.5 or 2. As initial sample size gets larger, stopping time gets earlier and its variation gets smaller. The coverage probabilities of treatment differences are reasonably close to the nominal level 0.95 and become closer to 0.95 as the initial sample size m_0 gets larger. Based on these findings, it is recommended that, in order to obtain earlier stable stopping time with a given precision satisfied, the initial sample size should not be too small.

When $\eta = 0$, correct treatment allocation probabilities are about 0.5, since it is equivalent to randomized allocation as there is no ethical consideration in the utility function. As η gets larger, correct treatment allocation gets better with similar performance for positive η . This confirms that η plays a role as a tuning parameter for ethical consideration and a, small, nonzero η is sufficient for correct allocation. Large correct allocation probabilities for positive η , in Table 1, illustrate that our sequential procedure under the CARA designs successfully implements the idea of CARA designs, with more allocation to better treatment, for the non-sequential counterpart.

For positive η , correct allocation is high and close to 0.9 when $T_0 = 1$ or when initial $T_0=0.5$ with varying T_0 . However, it is lower when $T_0 = 0.5$ with fixed T_0 compared to varying T_0 or when $T_0 = 2$ with varying T_0 compared to fixed T_0 . If T_0 varies depending on treatment effect variation, T_0 becomes larger than the initial T_0 . Thus, varying small T_0 gives better allocation due to the reasonable tuning size of T_0 , however, varying large T_0

gives worse allocation due to a too liberal tuning of T_0 . This emphasizes the importance of selecting a reasonably sized T_0 .

5. Discussion

In this paper, we propose a sequential estimation scheme for the CARA design in clinical trials. In this sequential estimation procedure, allocation function and design depend not only on previously collected information and sequential estimates of treatment effects, but also on the covariate information of individual subjects. The proposed sequential estimation is based on the martingale estimating equation, which differs from some classical sequential methods that rely on independent observations. The stopping rule used here depends on the observed Fisher information, which guarantees the precision of the estimates of treatment effects, and is novel in the CARA design based clinical trials. The procedure discussed here is rather general and can be applied to other generalized linear models. We demonstrate our method using some logistic regression models under a two-treatment case. The theorems derived in this work are for general allocation rules, which require only mild conditions on the allocation function. It will be possible to explore more if a specific allocation rule is available.

As shown in Figure 1, it is very difficult to allocate the most suitable treatment for subjects in the vicinity of the intersection of lines of two treatment effects. This is especially the case, when the difference in slopes of treatments is small. Thus, instead of a strictly concave function as we have used in our numerical study, some concave function with a plateau may be considered. According to our experience based on the numerical studies, the large changes adopted in T_0 during the sequential procedure may lower the correct allocation probability. Hence, from a practical viewpoint, a reasonably sized T_0 should be chosen in the utility function, considering all factors of a clinical trial, such as the distributions of covariates, the intersection point of the two treatment models and among others. In other words, if we have some prior information on the targeted subpopulations, then it may help to decide T_0 . This leads to possible future research, where Bayesian statistical tools might play an important role.

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Appendix A

To apply sequential sampling to CARA designs, we need to extend the results of Anscombe's theorem to daptive design. From the proof of Anscombe's theorem (see Woodroffe 1982, page 11), the i.i.d. assumption is not necessary; in fact, it only requires the sequence of partial sum to satisfy the u.c.i.p. condition. This is sufficient for applying Anscombe's theorem. The lemma below shows that the sequence of the partial sum of martingale differences also satisfies the u.c.i.p. condition. The arguments below are similar to those of Woodroffe (1982), example 1.8.

Lemma 1 *Let X_1, X_2, \dots be a sequence of martingale differences with respect to a sequence of increasing σ -field \mathcal{F}_i for $i = 0, 1, \dots$; that is, $E[X_i | \mathcal{F}_{i-1}] = 0$ for all $i \geq 1$. Suppose that there is a constant M such that $E[\|X_i\|^2 | \mathcal{F}_{i-1}] < M < \infty$ for all i . Then $Y_n = S_n^* = \sum_{i=1}^n X_i / \sqrt{n}$ satisfies the u.c.i.p. condition.*

Proof of Lemma 1

For all $k, n \geq 1$, $|S_{n+k}^* - S_n^*| \leq \sqrt{n} |S_{n+k} - S_n| + \left[1 + \sqrt{\frac{n}{n+k}}\right] |S_n^*|$, where $S_n = \sum_{i=1}^n X_i$. If $\epsilon, \delta > 0$ and $k \leq n\delta$, then the second term on the right hand side is bounded by $C(\delta)|S_n^*|$, where $C(\delta) = 1 - (1 + \delta)^{-1/2}$ and

$$P\left(C(\delta)|S_n^*| > \frac{\epsilon}{2}\right) \leq P\left(|S_n^*| > \frac{\epsilon}{2C(\delta)}\right) \rightarrow 0 \text{ as } \delta \rightarrow 0,$$

since $|S_n^*|$ is stochastically bounded. Because X_i 's are martingale differences, instead of Komogorov's inequality, we apply the Hájek-Rény inequality (see Chow and Teicher 1988, Theorem 8 (iii), page 247). Then it is shown that

$$P\left(\max_{k \leq n\delta} |S_{n+k} - S_n| \geq \frac{\epsilon\sqrt{n}}{2}\right) \leq \left(\frac{4}{n\epsilon^2}\right) n\delta M = \frac{4\delta M}{\epsilon^2},$$

which is independent of n and goes to zero as $\delta \rightarrow 0$. Therefore, S_n^* , $n \geq 1$, satisfies the u.c.i.p. condition.

A.1 Last time for generalized linear models

We can apply the last time method for martingale differences as that in Chang (1999) in our proof of asymptotic efficiency.

Let $\sigma_i^2 \equiv \text{Var}(Y_i|\boldsymbol{\xi}_i) = \sigma^2\nu(\mu_k)$. Then for fixed $\rho > 0$ and for each k , let's define a last time variable

$$L_{k,\rho} = \sup\{n \geq 1 : (\theta - \theta_k)' \ell_n(\theta) > 0 \exists \theta \in \partial\boldsymbol{\Theta}_{k,\rho}\},$$

where $\ell_{n,k}(\theta) = \sum_{i=1}^n g(\xi_i'\theta_k)\xi_i(Y_{i,k} - \mu_k(\theta_k, \xi_i))$ and $g(t) = \dot{\mu}_k/\nu(\mu_k)$, provided that the derivative of μ_k exists. Then it follows from Chang (1999),

$$n > L_{k,\rho} \Rightarrow \hat{\theta}_k \text{ exists and } \hat{\theta}_k \in \partial\boldsymbol{\Theta}_{k,\rho}.$$

Moreover, he proved that under some regularity conditions of covariate $\boldsymbol{\xi}$'s, $EL_{k,\rho} < \infty$ for all k . This implies that if we define the last time $L_\rho = \max\{L_{1,\rho}, \dots, L_{K,\rho}\}$, then $n > L_\rho$ implies that $\hat{\theta} \in \boldsymbol{\Theta}_\rho \subset \boldsymbol{\Theta}$, where $\boldsymbol{\Theta}_\rho = \prod_{k=1}^K \boldsymbol{\Theta}_{k,\rho}$.

Note that Chang (1999) defined last times for generalized linear models, and it is clear that for each $k \in \{1, \dots, K\}$, Equation (1) is a special case of Chang (1999). In Zhang et al. (2007), they assume the estimate of $\boldsymbol{\theta}$ exists in a compact set when sample size n is sufficiently large. By the last time defined above, since we can choose sufficiently small ρ such that for sufficiently large n , $\hat{\boldsymbol{\theta}}$ will fall into a compact neighborhood of $\boldsymbol{\theta}$. (Hence, the assumption of Zhang et al. (2007) can be relaxed. See Chang (1999) for further details).

Although the treatment allocation for each subject is affected by previous observed responses, it is clear that the estimate of θ_k , $k = 1, \dots, K$, is still calculated separately for a given sample under the general CARA design. Thus the estimation procedure of θ_k 's for all different k 's can be treated as estimating K adaptive regression models, separately. That is, for given observations, the estimation of θ_k , for each k , does not depend on estimates of other θ_l , $l \neq k$. That is, if for $k = 1, \dots, K$, let

$$U_{m,k} = \text{collection of observations } \{Y_{j,k}, \boldsymbol{\xi}_j \text{ with } X_{j,k} = 1 : j = 1, \dots, m\},$$

then the estimate of θ_k , say $\hat{\theta}_k$, is calculated based on observations in $U_{m,k}$ only. Thus, the

property of $\hat{\theta}_k$ is the same as the MLE of a stochastic regression model. The sequential estimate under the adaptive design has been studied by some authors. For example, Lai and Wei (1982) studied its properties under a linear regression setup with a general adaptive design assumption, while Chen et al. (1999), and Chang (2001) discussed estimation under a generalized linear model setup. Their results are applied in the proof of Theorem 1. (In these three papers, they only assume that the design is adaptive, but no particular design scheme is assumed. Hence, their methods are rather general and can be applied to our case under some specific allocation rules.)

Proof of Theorem 1

It is proved in Zhang et al. (2007) that $\hat{\mathbf{V}}$ is a strongly consistent estimate of \mathbf{V} . This implies that $\Lambda_{\max}(\hat{\mathbf{V}})$ and $\Lambda_{\min}(\hat{\mathbf{V}})$ are also strongly consistent estimates of $\Lambda_{\max}(\mathbf{V})$ and $\Lambda_{\min}(\mathbf{V})$, respectively. Thus, if $\sup_m \|\boldsymbol{\xi}_m\| < \infty$, then by Chow and Robbins (1965), Lemma 1, it is shown that $P(\tau_\delta < \infty) = 1$ and $\lim_{d \rightarrow 0} \tau_\delta / n_{opt} = 1$ with probability one and thus the proof of (i) is completed.

The highlight of the proof of (ii) is the asymptotic normality under the random sample size. This property can usually be obtained by applying Anscombe's Theorem, which relies on the u.c.i.p. property (see Woodroffe 1982). However, under the adaptive design, some modification is required. Thus, here we apply its modification, which is stated as Lemma 1.

The asymptotic normality of $\hat{\boldsymbol{\theta}}$ under the adaptive design has been established by Zhang et al. (2007) (see also Lai and Wei 1982, Chang 1999 and Chen et al. 1999). Following from the results of (i), to prove (ii), it suffices to prove that the sequence of normalized random sums $\{\sqrt{n}(\hat{\boldsymbol{\theta}}_n - \boldsymbol{\theta}), n \geq 1\}$ satisfies the u.c.i.p condition (see Woodroffe 1982 for its definition). From Equation (2.4) of Zhang et al. (2007), we have, with probability one, $\hat{\theta}_{n,k} - \theta_k = n^{-1} \sum_{m=1}^n X_{m,k} h_k(Y_{m,k}, \boldsymbol{\xi}_m)(1 + o(1)) + o(n^{-1/2})$, where function h_k satisfies $E[h_k(Y_k, \boldsymbol{\xi})|\boldsymbol{\xi}] = 0$.

It follows from Zhang et al. (2007) that we have

$$\sqrt{n}(\hat{\theta}_{n,k} - \theta_k) = n^{-1/2} \sum_{m=1}^n X_{m,k} h_k(Y_{m,k}, \boldsymbol{\xi}_m) + o(1) n^{-1/2} \sum_{m=1}^n X_{m,k} h_k(Y_{m,k}, \boldsymbol{\xi}_m) + o(1)$$

almost surely. It is clear that from the definition of u.c.i.p., the property of convergence with probability one will imply the property of u.c.i.p. Moreover, it follows from Lemma 1.4 of Woodroffe (1982), if both U_n and W_n are u.c.i.p., then $U_n + W_n$ is also u.c.i.p. By applying Lemma 1, we have that $\{n^{-1/2} \sum_{m=1}^n X_{m,k} h_k(Y_{m,k}, \boldsymbol{\xi}_m) : n \geq 1\}$ is u.c.i.p., which together with Lemma 1.4 of Woodroffe (1982) implies that $\{\sqrt{n}(\hat{\theta}_{n,k} - \theta_k) : n \geq 1\}$ satisfies the u.c.i.p. condition. Hence, applying Anscombe's theorem (Theorem 1.4 of Woodroffe (1982); see also Theorem 4.5.3 of Govindarajulu (2004)), the asymptotic normality of $\hat{\theta}_{n,k}$ remains for each k , and it completes the proof of (ii).

It follows from (i), that to prove (iii), it suffices to prove that $\{\delta\tau_\delta : \delta \in (0, 1)\}$ is uniformly integrable. As discussed in Section A.1,

$$n > L_\rho \Rightarrow \hat{\boldsymbol{\theta}}_n \in \boldsymbol{\Theta}.$$

Since $\boldsymbol{\Theta}$ is compact, this implies that for $n > L_\rho$, $\Lambda_{\max}(\hat{V}_k) \leq \sup_{\theta \in \boldsymbol{\Theta}} \Lambda_{\max}(V_k(\theta)) \leq C_{\Lambda_{\max}}$ for some $C_{\Lambda_{\max}} > 0$. Let $\tilde{V}_k = \text{diag}\{O, \dots, \hat{V}_k, \dots, O\}$ for $k = 1, \dots, K$, where O denotes the $p \times p$ matrix of 0's. Then $\hat{\mathbf{V}} = \sum_{k=1}^K \tilde{V}_k$. Thus, $\Lambda_{\max}(\hat{\mathbf{V}}) \leq \sum_{k=1}^K \Lambda_{\max}(\tilde{V}_k) \leq KC_{\Lambda_{\max}}$. Hence, for $n > L_\rho$, the stopping time τ_δ is bounded. Moreover, by applying the last time lemma for martingale differences in Chang (1999), we have $E[L_\rho] < \infty$. This implies that $\{\delta\tau_\delta : \delta \in (0, 1)\}$ is uniformly integrable and the proof of (iii) is completed.

The proofs of (iv) and (v) follow directly from Theorem 2.1, Equation (2.6) and Theorem 2.2, Equation (2.8) of Zhang et al. (2007) and the strong consistency of τ_δ , so they are omitted here. To prove (vi), we only need to show that $\{n^{-1/2}(\mathbf{N}_n - n\boldsymbol{\nu}) : n = 1, 2, \dots\}$ is u.c.i.p. From (A.6) of Zhang et al. (2007), we have, with probability one,

$$\mathbf{N}_n - n\boldsymbol{\nu} = \mathbf{M}_n + (1 + o(1)) \sum_{i=1}^n \sum_{k=1}^K \frac{T_{i,k}}{m} (\partial\boldsymbol{\nu} / \partial\theta_k)' + o(n^{1/2}),$$

where $\mathbf{M}_n = (\Delta M_{n,1}, \dots, \Delta M_{n,K})$ and $\mathbf{T}_n = (\Delta T_{n,1}, \dots, \Delta T_{n,K})$ are multi-dimensional martingale sequences with bounded martingale differences; that is, $\Delta M_{n,k} \leq 1$ and $\|\Delta \mathbf{T}_{n,k}\| < \infty$, where Δ denotes the operand of a sequence $\{z_n\}$; that is, $\Delta z_n = z_n - z_{n-1}$. (Here only the moment condition of martingale differences is required for our purpose.

Thus, other properties of \mathbf{M}_n and \mathbf{T}_n are omitted. See Zhang et al. (2007) for further details.) Therefore, with probability one,

$$n^{-1/2}(\mathbf{N}_n - n\boldsymbol{\nu}) = n^{-1/2}\mathbf{M}_n + (1 + o(1))n^{-1/2} \sum_{i=1}^n \left[\sum_{k=1}^K \frac{T_{i,k}}{m} (\partial\boldsymbol{\nu}/\partial\theta_k)' \right] + o(1).$$

Similarly, by applying Lemma 1 again and arguments similar to Woodroffe (1982), Example 1.8, we have $\{n^{-1/2}(\mathbf{N}_n - n\boldsymbol{\nu}) : n = 1, 2, \dots\}$ is u.c.i.p. This completes the proof of Theorem 1 (vi).

Proof of Theorem 2

By the definition of $\boldsymbol{\gamma} = H'\boldsymbol{\theta}$ and $\text{rank}(H) = h \leq p$, it is easy to see that $\hat{\boldsymbol{\gamma}}$ is a strongly consistent estimate of $\boldsymbol{\gamma}$ and is asymptotically normally distributed with covariance matrix $V_{\boldsymbol{\gamma}}$. Moreover, it is clear that $\{\sqrt{n}(\hat{\boldsymbol{\gamma}}_n - \boldsymbol{\gamma}) : n = 1, 2, \dots\}$ is u.c.i.p., since H is a non-random matrix. Thus, the proofs of Theorem 2 (i) and (ii) follow from the same arguments as in the proofs of Theorem 1 (i) and (ii). To prove (iii), we first note that by simple matrix algebra, we have

$$\Lambda_{\max}(\hat{\mathbf{V}}_{\boldsymbol{\gamma}}) = \Lambda_{\max}(H'\hat{\mathbf{V}}H) \leq \Lambda_{\max}(H'H) \cdot \Lambda_{\max}(\hat{\mathbf{V}}).$$

Since H is a pre-fixed non-random matrix, $\Lambda_{\max}(H'H) (= \lambda_H, \text{ say})$ is a constant. Now, let

$$\tilde{\tau}_{\delta_{\boldsymbol{\gamma}}} = \inf\{n \geq n_0 : n \geq \lambda_H \frac{C_{\alpha, \boldsymbol{\gamma}}^2 \Lambda_{\max}(\hat{\mathbf{V}}_{\boldsymbol{\gamma}})}{\delta_{\boldsymbol{\gamma}}^2}\}.$$

Then by definition, we have $\tau_{\delta_{\boldsymbol{\gamma}}} \leq \tilde{\tau}_{\delta_{\boldsymbol{\gamma}}}$ almost everywhere. Moreover, again it can be shown by the same arguments above that $\{d^2 \tilde{\tau}_{\delta_{\boldsymbol{\gamma}}} : d \in (0, 1)\}$ is uniformly integrable. This implies that $\{d^2 \tau_{\delta_{\boldsymbol{\gamma}}} : d \in (0, 1)\}$ is uniformly integrable and thus the proof of (iii) of Theorem 2 is completed.

References

- Albert, A. (1966). Fixed size confidence ellipsoids for linear regression parameters. *Ann. Math. Statist.* 37, 1602 – 1630.
- Bandyopadhyay, U. and A. Biswas (2001). Adaptive designs for normal responses with prognostic factors. *Biometrika* 88, 409 – 419.
- Bandyopadhyay, U., A. Biswas, and R. Bhattacharya (2007). A covariate adjusted two-stage allocation design for binary responses in randomized clinical trials. *Statistics in Medicine* 26(24), 4386 – 4399.
- Bandyopadhyay, U. and S. De (2009). Two-treatment covariate-dependent response adaptive allocation design for dichotomous response. *Journal of the Korean Statistical Society* 38, 157 – 165.
- Chang, Y.-c. I. (1999). Strong consistency of maximum quasi-likelihood estimate in generalized linear models via a last time. *Statistics & Probability Letters* 45, 237 – 246.
- Chang, Y.-c. I. (2001). Sequential confidence regions of generalized linear models with adaptive designs. *Journal of Statistical Planning and Inference* 93, 277 – 293.
- Chen, K., I. Hu, and Z. Ying (1999). Strong consistency of maximum quasi-likelihood estimators in generalized linear models with fixed and adaptive designs. *Ann. Statist.* 27(4), 1155–1163.
- Chow, Y. S. and H. Robbins (1965). On the asymptotic theory of fixed-width sequential confidence intervals for the mean. *The Annals of Mathematical Statistics* 36(2), 457 – 462.
- Chow, Y. S. and H. Teicher (1988). *Probability Theory* (2 ed.). New York, USA: Springer.
- Ghosh, B. K. and P. K. Sen (1991). *Handbook of Sequential Analysis*. New York: Marcel Dekker, Inc.
- Govindarajulu, Z. (2004). *Sequential Statistics*. World Scientific.

- Hu, F. and W. F. Rosenberger (2006). *The Theory of Response-Adaptive Randomization in Clinical Trials*. Wiley Series in Probability and Statistics. London, UK: John Wiley & Sons.
- Lai, T. L. and C. Z. Wei (1982). Least squares estimates in stochastic regression models with applications to identification and control of dynamic systems. *The Annals of Statistics* 10(1), 154–166.
- McCullagh, P. and J. A. Nelder (1989). *Generalized Linear Models* (2 ed.). London, UK: Chapman and Hall.
- Moler, J. A., F. Plo, and M. S. Miguel (2006). An adaptive design for clinical trials with non-dichotomous response and prognostic factors. *Statistics and Probability Letters* 76, 1940 – 1946.
- Siegmund, D. (1985). *Sequential Analysis: Tests and Confidence Interval*. New York: Springer-Verlag.
- Simon, E. and A. Maitournam (2005). Evaluating the efficiency of targeted designs for randomized clinical trials. *Clinical Cancer Research* 10, 6759 – 6763.
- Thall, P. F. and J. K. Wathen (2005). Covariate-adjusted adaptive randomization in a sarcoma trial with multi-stage treatments. *Statistics in Medicine* 24, 1947 – 1964.
- Woodroffe, M. (1982). *Nonlinear Renewal Theory in Sequential Analysis*. Society for Industrial and Applied Mathematics, Philadelphia, Pennsylvania.
- Zelen, M. and L. J. Wei (1995). *Foreword*. In *Adaptive Designs*. Hayward, CA: IMS.
- Zhang, L. and F. Hu (2009). A new family of covariate-adjusted response adaptive designs and their properties. *Appl. Math. J. Chinese Univ.* 24(1), 1 – 13.
- Zhang, L., F. Hu, S. Cheung, and W. Chan (2007). Asymptotic properties of covariate-adjusted response-adaptive designs. *Annals of Statistics* 35(3), 1166 – 1182.

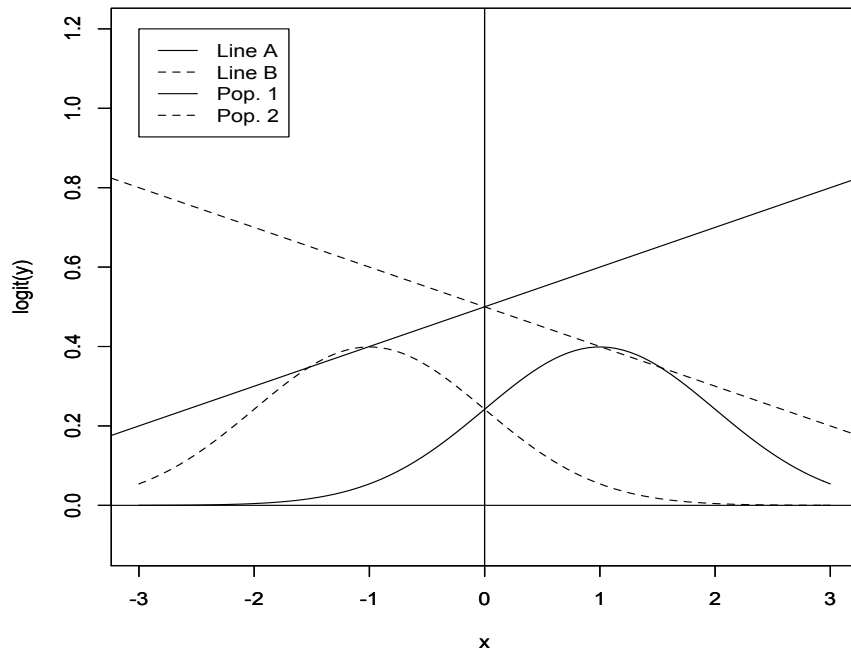


Figure 1: Sequential CARA design with two treatment slopes and two covariate populations.

Table 1: Mean (M) and standard deviation (SD) of stopping time (τ_{δ_γ}), coverage probability (CP) and correct allocation probability (CAP) of sequential 95% confidence interval estimation with $\delta = 0.3$. T_{0V} and η_V indicate whether T_0 and η vary or not

m0	T ₀	η	Variation		τ _{δ_γ}				m0	T ₀	η	Variation		τ _{δ_γ}			
			T _{0V}	η _V	M	SD	CP	CAP				T _{0V}	η _V	M	SD	CP	CAP
5	0.5	0.0	N	N	53	9	0.95	0.48	10	1.0	0.1	Y	Y	60	11	0.96	0.87
5	0.5	0.0	Y	N	58	24	0.90	0.46	10	1.0	1.0	N	N	60	11	0.98	0.92
5	0.5	0.1	N	N	67	21	0.94	0.76	10	1.0	1.0	N	Y	63	14	0.96	0.92
5	0.5	0.1	N	Y	67	23	0.93	0.74	10	1.0	1.0	Y	N	65	16	0.98	0.93
5	0.5	0.1	Y	N	76	34	0.92	0.88	10	1.0	1.0	Y	Y	63	14	1.00	0.93
5	0.5	0.1	Y	Y	66	16	0.97	0.87									
5	0.5	1.0	N	N	83	59	0.92	0.76	10	2.0	0.0	N	N	55	14	0.92	0.47
5	0.5	1.0	N	Y	70	33	0.95	0.77	10	2.0	0.0	Y	N	52	14	0.97	0.46
5	0.5	1.0	Y	N	81	20	0.96	0.91	10	2.0	0.1	N	N	59	13	0.96	0.83
5	0.5	1.0	Y	Y	75	18	0.96	0.91	10	2.0	0.1	N	Y	57	12	0.99	0.83
									10	2.0	0.1	Y	N	54	12	0.96	0.76
5	1.0	0.0	N	N	53	13	0.96	0.50	10	2.0	0.1	Y	Y	56	10	0.97	0.77
5	1.0	0.0	Y	N	54	13	0.94	0.49	10	2.0	1.0	N	N	62	18	0.95	0.87
5	1.0	0.1	N	N	69	17	0.92	0.87	10	2.0	1.0	N	Y	66	22	0.92	0.88
5	1.0	0.1	N	Y	68	15	0.96	0.85	10	2.0	1.0	Y	N	58	12	1.00	0.84
5	1.0	0.1	Y	N	66	15	0.96	0.84	10	2.0	1.0	Y	Y	57	14	0.96	0.83
5	1.0	0.1	Y	Y	66	16	0.86	0.84									
5	1.0	1.0	N	N	75	19	0.96	0.91	15	0.5	0.0	N	N	52	10	0.98	0.50
5	1.0	1.0	N	Y	77	18	0.98	0.91	15	0.5	0.0	Y	N	51	9	0.96	0.45
5	1.0	1.0	Y	N	72	13	0.96	0.90	15	0.5	0.1	N	N	52	9	0.98	0.72
5	1.0	1.0	Y	Y	73	19	0.99	0.90	15	0.5	0.1	N	Y	53	10	0.98	0.74
									15	0.5	0.1	Y	N	58	12	0.98	0.87
5	2.0	0.0	N	N	54	11	0.90	0.48	15	0.5	0.1	Y	Y	55	14	0.98	0.90
5	2.0	0.0	Y	N	53	10	0.94	0.49	15	0.5	1.0	N	N	54	10	1.00	0.75
5	2.0	0.1	N	N	60	14	0.99	0.79	15	0.5	1.0	N	Y	54	18	0.98	0.76
5	2.0	0.1	N	Y	61	14	0.96	0.79	15	0.5	1.0	Y	N	57	20	0.94	0.90
5	2.0	0.1	Y	N	54	10	0.98	0.73	15	0.5	1.0	Y	Y	56	18	0.96	0.89
5	2.0	0.1	Y	Y	57	13	0.94	0.72									
5	2.0	1.0	N	N	73	20	0.91	0.86	15	1.0	0.0	N	N	52	9	0.96	0.50
5	2.0	1.0	N	Y	71	18	0.97	0.88	15	1.0	0.0	Y	N	52	10	0.97	0.43
5	2.0	1.0	Y	N	59	14	0.96	0.80	15	1.0	0.1	N	N	56	11	0.98	0.91
5	2.0	1.0	Y	Y	57	11	0.98	0.78	15	1.0	0.1	N	Y	55	13	0.98	0.90
									15	1.0	0.1	Y	N	55	11	0.98	0.92
10	0.5	0.0	N	N	52	8	0.92	0.48	15	1.0	0.1	Y	Y	53	12	0.96	0.91
10	0.5	0.0	Y	N	52	10	0.92	0.46	15	1.0	1.0	N	N	54	11	0.96	0.91
10	0.5	0.1	N	N	58	12	0.96	0.74	15	1.0	1.0	N	Y	58	18	0.96	0.93
10	0.5	0.1	N	Y	59	16	0.98	0.75	15	1.0	1.0	Y	N	57	12	0.94	0.95
10	0.5	0.1	Y	N	63	14	0.96	0.90	15	1.0	1.0	Y	Y	56	10	0.98	0.95
10	0.5	0.1	Y	Y	61	13	1.00	0.91									
10	0.5	1.0	N	N	57	13	0.99	0.78	15	2.0	0.0	N	N	52	9	0.97	0.49
10	0.5	1.0	N	Y	57	14	0.97	0.74	15	2.0	0.0	Y	N	52	9	0.96	0.44
10	0.5	1.0	Y	N	64	16	0.93	0.92	15	2.0	0.1	N	N	55	15	0.96	0.88
10	0.5	1.0	Y	Y	61	12	0.98	0.92	15	2.0	0.1	N	Y	54	11	1.00	0.84
									15	2.0	0.1	Y	N	53	10	0.97	0.83
10	1.0	0.0	N	N	54	11	0.92	0.46	15	2.0	0.1	Y	Y	50	8	0.96	0.79
10	1.0	0.0	Y	N	52	9	0.96	0.47	15	2.0	1.0	N	N	59	15	0.98	0.90
10	1.0	0.1	N	N	63	16	0.98	0.90	15	2.0	1.0	N	Y	54	12	0.95	0.88
10	1.0	0.1	N	Y	62	17	0.94	0.87	15	2.0	1.0	Y	N	55	12	0.98	0.86
10	1.0	0.1	Y	N	63	14	0.96	0.89	15	2.0	1.0	Y	Y	53	13	0.98	0.85